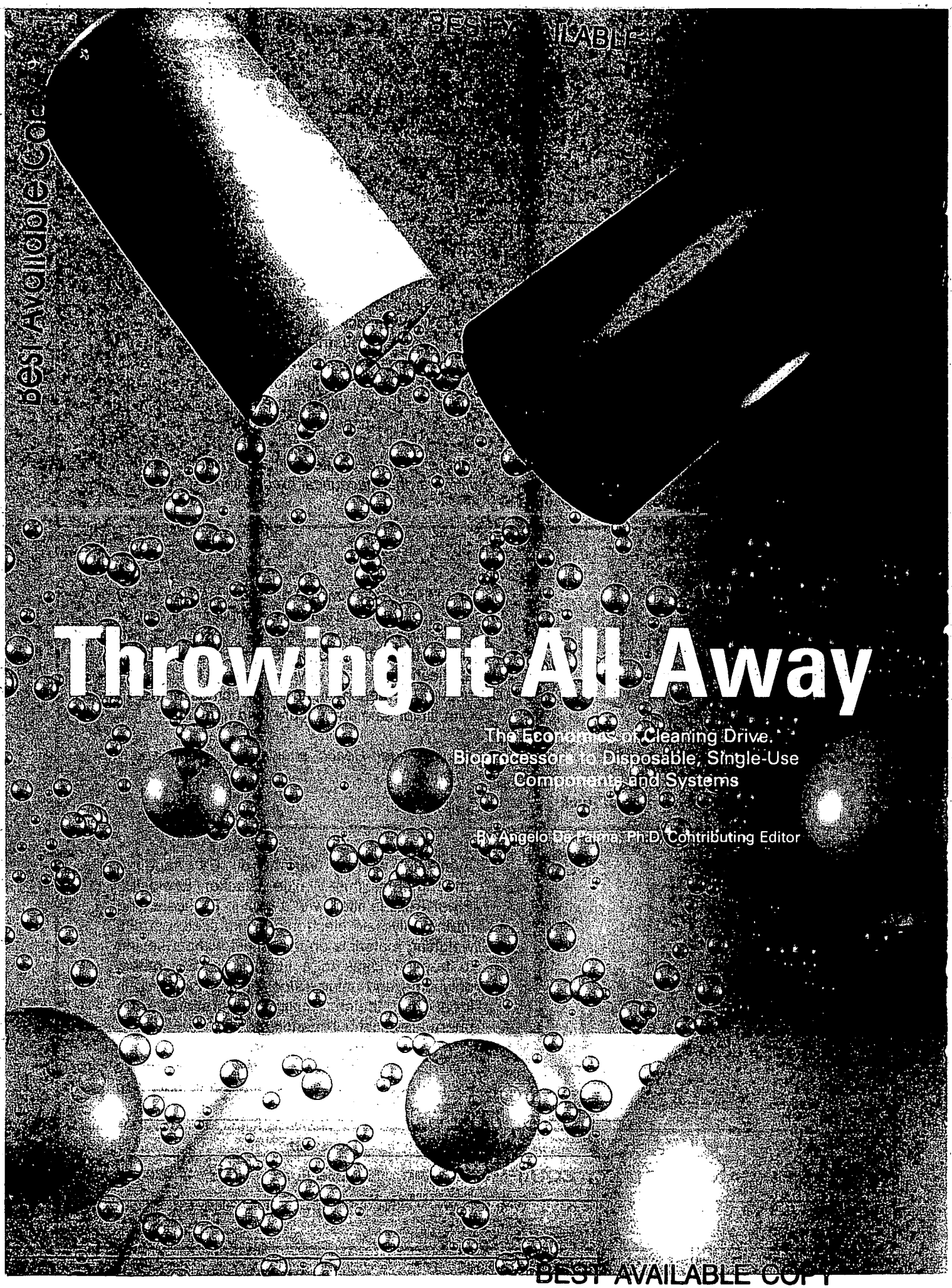

Throwing it All Away

The Economics of Cleaning Drive Bioprocessors to Disposable, Single-Use Components and Systems

By Angelo DePalma, Ph.D. Contributing Editor

In their quest for efficiency, versatility and lower costs, biomanufacturers are putting their stainless steel reactors and storage vessels into mothballs and turning to single-use plastic equipment. Replacing steel with plastic is hardly a new idea, but for biopharmaceutical companies, the switch is nothing short of revolutionary.

Disposability supports biotech's need for leaner, safer, more agile manufacturing. Cleaning and cleaning validation are practically eliminated wherever disposable bags, filters and tubing replace stainless. Costs associated with cleaning materials, lost production time, scheduling inefficiencies, and time restraints for sterilization and steam-and-hold become passé.

Disposables resolve potential product segregation issues because contact surfaces see one product, one time, before they're discarded. And although few new facilities specify disposable processing during design, doing so could save millions in capital expenditures for water and steam plants, not to mention bioreactors and fermenters.

The seeds for disposable biomanufacturing were sown in the blood products industry, where multiple-product facilities are common and safety reigns supreme. In biotech, especially at contract manufacturers, disposables address "myriad issues" for non-dedicated manufacturing sites, says Greg Page, Ph.D., pharmaceutical life science practice leader at Deloitte (Jericho, NY).

Ever since biotech caught the disposables bug, processing "in plastico" has spread horizontally and vertically into various niches through the process chain. Plastic bags replaced steel tanks for media and buffer storage, then morphed into mixing containers and bioreactors. Plastic tubing, valves and connectors encroached on stainless steel pipes and manifolds. Membrane filters appeared housed in single-use cartridges. Downstream, disposable membrane chromatography cartridges replaced some ion exchange resins, while process engineers rethought the economics of cleaning and validating even expensive resins. In short, the high value of biotech products provides fertile ground for disposable manufacturing.

Many disposable products evolved in stages. Neil Holman of Millipore cites ultrafiltration as an example. First came cleanable filters, then disposable filters in stainless steel holders. "As filters became higher-performing, it made sense to enclose smaller-area membranes completely in plastic," Holman notes. The newer filter units, individually too small for large processes, were manifolded together and *voilà*: A completely disposable filter operation.

Disposability's greatest benefits are evident with batches of up to about 1,000 liters, bucking biotech's yen for huge bioreactors. Economies of scale and the success of high-dose monoclonal antibody therapies have pushed bioreactor sizes well above 20,000 liters.

Yet several factors could reverse the bigger-is-better trend in commercial cell culture, making disposables even more indispensable. Therapeutic trends in favor of smaller, disposable processes include personalized medicine; treatments based on genotyping, gene and viral therapy, and radioimmunotherapy all rely on smallish batches. The biggest boost for smaller batches, however, will come from improved volumetric productivity (product per volume of culture fluid), which has already increased at least fifty-fold in the past two decades. Higher productivity equals smaller batches, a boon to disposables.

Plastic Has its Limits

Fully-disposable large-scale processing is probably a few years away. Its arrival will depend on manufacturers adopting disposables early, and carrying the idea forward during scale-up and process development. But even when the "big disposable" arrives, it will not be appropriate for every manufacturer. Large-scale fermentations will probably not benefit any time soon, since process bags are limited to about 2,000-liter volumes. Similarly, already-approved processes are unlikely to switch over. Non-biotech drugmakers, whose processes often employ organic solvents, high heat and caustic reagents, will probably avoid plastics altogether.

"It's unlikely that disposable reactors will replace ten- or twenty-thousand liter stainless steel reactors any time soon," predicts Maik Jornitz, group vice president at Sartorius . North America (Edgewood, N.Y.). "Mixing and process control are serious concerns in plastic reactors and exemplify the design benefits of stainless steel fermenters," Jornitz says. "Mixing device and gas distribution determine whether cells thrive or die."

A related roadblock, according to Vijay Singh, Ph.D., CEO of Wave Biotech (Bridgewater, N.J.) is the dearth of throw-away instrumentation for monitoring culture pH, dissolved oxygen, turbidity and conductivity. Singh believes instrument makers eventually will catch up, perhaps with optical detection and microprocessor control, which could eliminate end-user calibration. "Medicine has been using such devices for years," Singh says.

Even as storage vessels, 5,000 liters may be the upper limit for plastic containers, at least with current bag-making technology. Stedim Inc. (Concord, Calif.), which claims to be the only biobag producer that casts its own plastic film, manufactures its larger bags from four plastic sheets heat-sealed at the edges. End-users may be concerned about the structural integrity of very large bags, even when they're supported by steel holding tanks. Plus, as Stedim marketing manager Greg Ja notes, "Above about 5,000 liter capacity bags get quite heavy. You need special equipment just to lift them without damaging them."

Disposable products still require validation, which vendors typically provide, for materials, sterility, leaching and extractables. Process designers also must specify interconnectivity among plastic components with disposable valves, connectors and tubing. All such products carry a measurable validation overhead, which, depending on the application, may be compounded by multiple-vendor sourcing.

Connectivity is a basic, enabling technology for disposables so users must carefully specify connectors, ports and valves, especially under sterile conditions. Many

firms offer kits and tools for creating almost any type of connection between throwaways and the rest of the process. Kleenpak filter capsules from Pall (East Hills, N.Y.) use proprietary mechanical connections; Wave Biotech sells a sterile tubing welder and a portable tube sealer; Millipore (Billerica, Mass.) has introduced preassembled, presterilized connectors. Many companies offer pinch valves for flexible tubing, among them Thomas Ladisch Associates (Gilbertsville, Pa.), which sells both manual and actuated versions.

JVs Drive Innovation

Joint ventures have thus far been the lifeblood of disposable manufacturing innovation. All major container manufacturers have ongoing agreements that add functionality to their "biobags." For example, Stedim collaborates with Integrated Biosystems (Napa, Calif.) on freezing applications, with Sweden's Pharmadule on design of rigid-vessel equipment and disposable bags, and with yet another firm on sanitary ports. TC Tech (Maple Plain, Minn.) obtains disposable process vessels from Stericon (Broadview, Ill.) and supplies 200-liter bags for the disposable, magnetically-levitated mixing system of LevTech (Lexington, Ky.).

Sartorius' involvement in disposability includes sterile and pre-filtration, membrane chromatography, storage/holding bags (through an alliance with TC Tech), fully assembled bag/filter devices, and crossflow micro-and ultra- filtration as single-use cassettes. The company is working in a two-prong approach: fully disposable processing and fully integrated large-scale engineered processes. Sartorius has invested in process know-how and engineering talent, in addition to building a new facility for its Sartorius BBI Systems (Allentown, Pa.; formerly B. Braun) bioprocess subsidiary.

Xcellerex (Marlborough, Mass.) takes a similar, big-picture approach to disposables. While still a part of Millennium Pharmaceuticals before being spun off three years ago, Xcellerex was charged with creating a flexible, affordable manufacturing platform to support clinical trials. The company's core technologies included isolators, automation and controls, and disposables—the "key piece" according to technology vice president Geoffrey Hodge. "By relying as much as possible on disposables, we've practically eliminated the need for utilities," Hode says. "We still need electricity and gases, and not every operation is disposable, but we can operate without clean steam, plant steam, WFI loops, and CIP/SIP systems."

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Collaborations go well beyond equipment swaps, as companies seek partners with scientific or engineering capabilities. Millipore has teamed with culture media specialist HyClone Laboratories (Logan, Utah) on the design, development, and validation support for disposable manufacturing. Like most of these joint ventures, one side (HyClone) provides plastic bag technology (up to 1,500 liters) while the other (Millipore) offers a value-added component, in this case filtration. Hynetics, the joint venture between Hyclone and Alfa Laval's Biokinetics subsidiary (Philadelphia), is implementing a broad disposable manufacturing approach. Called "One-Touch Bioprocessing," the initiative is based on the notion that all bioprocess surfaces should be disposable.

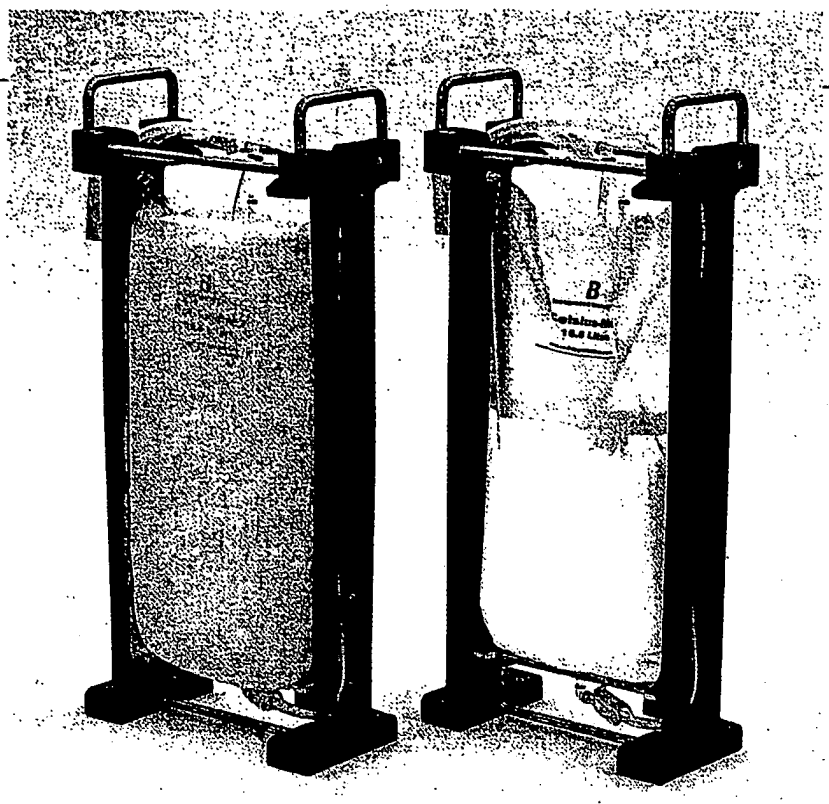
Categorically, these collaborations aim to add value by addition and integration of technologies, strategies, and even disciplines. "The synergies in these partnerships provide end-users with value they could not obtain from those vendors individually," says John Schmitz of TC Tech.

A Flock of Niches

Niche applications dominate single-use markets today. Although all the components of a turnkey, fully-disposable process probably don't exist in integratable form, it's only a matter of time before someone puts the pieces together.

Integrated Biosystems, which specializes in freeze-thaw equipment, extended its reach into disposables in June, 2003, with the introduction of its single-use Celsius disposable freezing bag product line (photo). Celsius, which is scalable up to 100 liters, gives small-batch manufacturers the additional flexibility of freezing process fluids until downstream capacity opens up.

A hundred liters may be small at the fermentation level, but it's substantial for finished product just before fill. "Although bioreactors are growing in size, a typical final API volume is typically between 100 and 300 liters," says CEO John Brown. The first major customer for Celsius uses 16.6-liter bags to store up to 2,000 liters of process fluid during a "hold" step.



Integrated Biosystems has found a disposable niche providing "holding tanks" for in-process fluids. Materials are frozen (left) in 16.6 L bags while awaiting downstream processing capacity to open up.

Being a bag manufacturer, instead of simply a distributor, has its advantages vis-à-vis new application development. For example, Stedim, which supplies freeze-thaw bags to Integrated Biosystems, now offers a plastic process container thermoregulated by a jacketed, form-matched, variable-temperature stainless steel tank. Greg Ja describes the tank, which holds buffers or media at typical process or storage temperatures, as a "miniature cold room"—without the room, of course.

Fermentation and cell culture are perhaps the killer apps of disposable biotech. Only one supplier, Wave Biotech (Bridgewater, N.J.) offers a plastic bag-based bioreactor large enough to be considered production-worthy. The Wave Bioreactor cell culture system handles volumes of up to 500 liters and includes bags, a rocking table for agitation/aeration, and associated tubing and connectors. The LevTech DB-200 magnetically levitated mixer mentioned earlier has many features desirable in a disposable bioreactor but the magnetically levitated impeller evidently does not provide enough torque for stirring a large tank of cells. Recognizing the potential for plastic bioreactors, however, codevelopers TC Tech and LevTech are working on other stirring applications, including disposable fermenters and bioreactors.

In contrast to LevTech's non-contact stirring mechanism, Hyclone's Mixtainer disposable mixing system uses a disposable bag fitted with a disposable magnetic stir bar. Through its Hynetics subsidiary, Hyclone also offers a mixing system that uses a disposable polyethylene impeller. Hynetics' crown jewel, however, is a completely disposable sterile formulation system that scales up to 10,000 liters.

Product Values Warp Downstream Economics

Chromatography is not usually thought of as disposable due to high resin costs. "Capture" chromatography, used to isolate crude monoclonal antibodies, still relies on frighteningly expensive Protein A affinity media. Synthetic and recombinant replacements for Protein A are in

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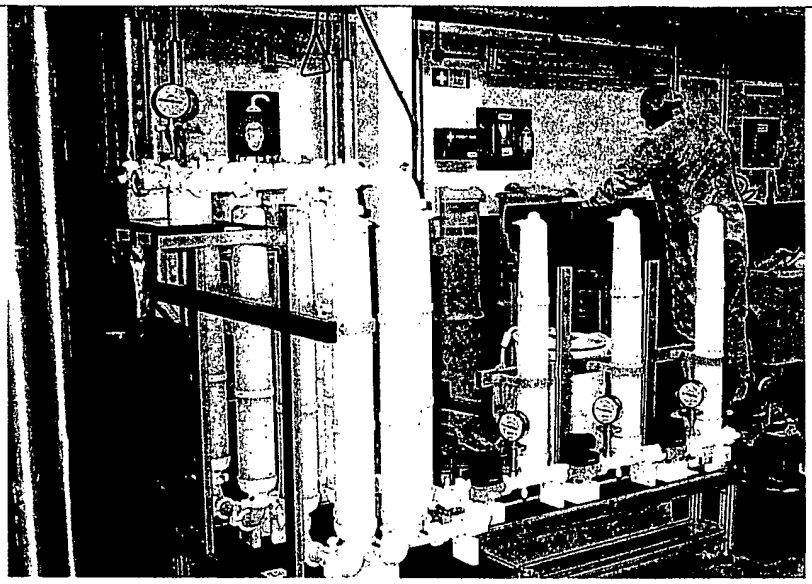
development, which should promote the idea of disposable capture media. But for now, antibody capture represents the immovable object in the path of the disposables juggernaut.

Even so, biotech is rethinking the benefits of reusing even expensive materials like affinity media. Maik Jornitz of Sartorius believes that it may make sense to discard even costly capture resins if the economics dictate. "Disposability depends on the value of your product," he observes. "Processors may be losing yield on Protein A columns due to the lengthy processing time, and that's before factoring in cleaning and cleaning validation costs. If a product is of high enough value, the resin may indeed turn out to be expendable."

Jornitz points out that the quite acceptable (and conservative) loss of one percent of a $10 million batch attributable to column reuse or long on-column residence translates to a loss of $100,000 worth of product. "And a one percent loss is nothing in bioprocessing," Jornitz says. "Depending on the process design and the equipment used, losses in the downstream process are commonly higher."

Jornitz believes that downstream process optimization could change the economics of disposability as well as reducing capacity requirements and overall manufacturing costs. "Everyone is talking about the capacity crunch, but optimizing downstream processing would eliminate a lot of the crunch issues. It's unreal how much product is lost downstream. Losses will always happen, but they can be reduced by optimizing the design and using up-to-date downstream tools, for example membrane chromatography, low-binding ultrafiltration and sterile filtration membranes."

Disposable ion exchange membrane chromatography is already in approved processes to complement classical gel chromatography in the removal of host cell DNA/RNA and endotoxins. Although the membranes have limited capacity, end-users work around this by multiplexing several units together. Membrane chromatography products from Pall, Millipore, and Sartorius are replacing polishing ion exchange columns rapidly due to the membranes' ultra-fast process times. "With a one-liter membrane ion exchanger replacing 150 liters of resin, you're saving not just on media, but on buffer," notes Millipore's Richard Pearce.



A growing number of bioprocessors are finding disposable equipment an indispensable tool. Here, a technician works with disposable filtration modules.

Implementation Piecemeal—for Now

Disposable biomanufacturing is growing in scale as well as appeal. "It's no longer outlandish to envision entirely disposable processes," says Holly Haughney, Ph.D., vice president of biopharmaceutical marketing for Pall. But before that day arrives, end-users will need to justify piecemeal implementations based on costs. Vendors make a compelling case for cost savings, but, in the end, companies must do their own math.

Increasingly, that calculation will incorporate rising drug costs as well as manufacturing efficiencies, which are, after all, two sides of the same coin.

"Manufacturers used to say 'So what if it costs $200 a dose? It's not my problem,'" say Tom Ladisch of Thomas Ladisch Associates. "The reason drugs cost that much is because cost has traditionally not been a factor during plant design." Only through scrutiny of facility costs, he believes, will disposables routinely be specified in design plans. "Today, disposability is not proactively designed in. It only enters the picture after construction, when people can't figure out another way to do something."

Whether disposability settles into niche-only applications or is adopted industry-wide for a majority of processes depends on vendors' ability to match products with immediate needs, and to stay ahead of the process innovation curve. From vendors, large-scale disposable processing requires larger systems and components, throwaway monitoring and controls, and process-worthy stirring and agitation. To join the dance, end-users need to achieve process efficiencies and shrink process volumes. More compact operations can tip the scales, particularly in downstream operations, in favor of disposables.

So far, vendors are doing their part, as the cost of single-use plastic equipment falls through competition, improved manufacturing and greater sales volumes. Validation groups at biopharm companis are contributing to the plastics revolution as well, albeit unwittingly, by fostering a validation environment which Wave CEO Vijay Singh has described as a "multi-headed monster." Eventually, says Singh, biomanufacturers may adopt disposables if for no other reason than "that may be the only way for them to get their jobs done."